

Retinal oxalosis

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Deposition of calcium oxalate crystals in the eye, though not common, is possibly not so rare as the small number of published reports would indicate. Most often it is associated with long-standing degenerative change and as such has been described in conjunction with detached retinae (Cogan, Kuwabara, Silbert, Kern, McMurray, and Hurlbut, 1958; Zimmerman and Johnson, 1958; Friedman and Charles, 1974) and cataractous lenses (Zimmerman and Johnson, 1958). According to Williams and Smith (1972), ocular involvement in primary hyperoxaluria is extremely unusual; of the two reports in the literature, one concerns a man with scanty crystals in the ciliary body detected *post mortem* (Scowen, Stansfeld, and Watts, 1959), and the other relates to a boy with presumed calcium oxalate crystals in the macular region of the retinae found by ophthalmoscopy (Buri, 1962). Bullock, Albert, Galla, Skinner, and Miller (1973) have recently described the presence of oxalate in the pigment epithelium of the retinae of a man dying from oxalosis attributable to prolonged methoxyflurane anaesthesia, but otherwise there are no reports of the eye being implicated in secondary hyperoxaluria.

In the vast majority of instances oxalate deposition in the eye is, therefore, a purely ocular disturbance, the aetiology and pathogenesis of which is almost totally obscure. The object of the present report is to document a further case of oxalate formation associated with retinal detachment and to discuss some of the factors which might be of aetiological significance.

Case report

The patient was a young man of Pakistani parentage who lived in Southern England.

At the age of 13 years he had been hit in the eye by a foreign body composed of a hard plastic material and sustained a perforating injury to the cornea. This was complicated by secondary retinal detachment and eventually the eye became atrophic and shrunken. Pain, related to recurrent attacks of uveitis, ultimately necessitated enucleation of the now completely blind eye at the age of 21 yrs. The remaining (right) eye was quite normal, with unimpaired vision, and there was no family history suggestive of oxalosis.

Ocular pathology

MACROSCOPICAL

The globe was shrunken and the anterior segment was disorganized as a result of extensive scar tissue formation around a retained foreign body composed of a green and white plastic

substance. The retina was completely detached with numerous crystalline structures resembling stalactites projecting from its outer layers into the underlying gelatinous subretinal exudate (Fig. 1).

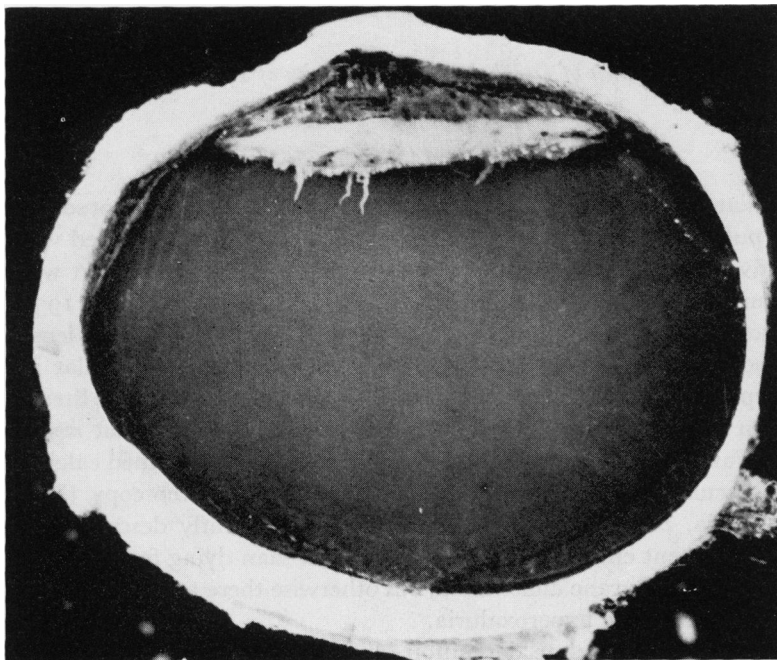


FIG. 1 Calotte of the eye opened in a horizontal plane, showing the periphery of a detached retina from which crystalline masses are projecting into an underlying proteinaceous exudate. $\times 9$

MICROSCOPICAL

The cornea was scarred and vascularized with evidence of a healed central perforation; some calcification of the superficial collagen was also seen. Immediately deep to the wound was a plaque of fibrous scar tissue which extended over the anterior surface of a mildly inflamed iris and was responsible for binding the iris margins to the back of the cornea. Behind the iris was a fibrous cyclitic membrane, in which were incarcerated some folded remnants of the ruptured lens capsule and a small cavity which had contained the foreign body seen on gross examination (Fig. 2). A number of giant cells and macrophages were seen in the immediate vicinity of the foreign body. The retina was degenerate and disorganized as well as being completely detached and adherent to the cyclitic membrane. The resultant subretinal space was filled with serous exudate, and extending into it from the outer layers of the retina were numerous crystalline aggregates (Fig. 3). A minor degree of chronic inflammation was present in the choroid and ciliary body and was associated with some reactive hyperplasia in the ciliary pigment epithelium. The optic nerve was atrophic and showed replacement gliosis, while the surrounding choroid included an area of ossification.

ANALYSIS OF CRYSTALS

The crystals were strongly birefringent (Fig. 4) and appeared as colourless elongated structures grouped together in sheaves. They were insoluble in 2N acetic acid and were weakly stained by the von Kossa method. In contradistinction to the phosphate and

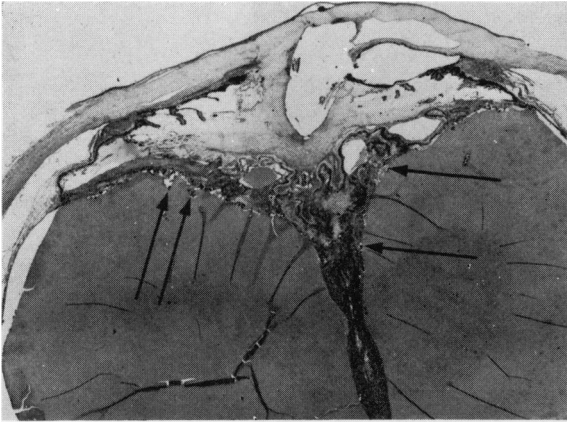


FIG. 2 Section of part of the eye, showing disorganization of the anterior segment by extensive post-traumatic fibrosis: a space in the scar tissue was originally occupied by a retained foreign body. The retina is completely detached and bound to the posterior surface of the fibrosed anterior segment, while clusters of crystals have formed on its deep surface (arrowed). $\times 7$

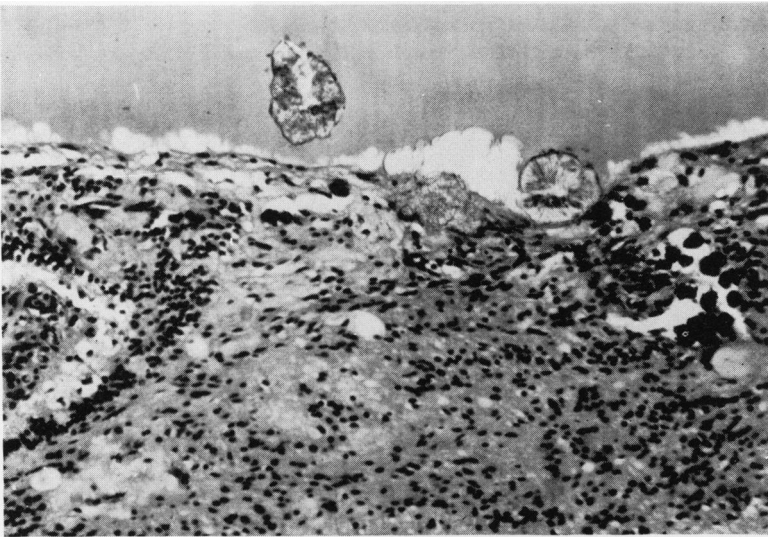


FIG. 3 Section of part of the disorganized and detached retina, showing the presence of crystalline aggregates on the outer surface. Scattered granules of melanin derived from degenerate pigment epithelium are also to be seen. $\times 180$

carbonate salts of calcium, they reacted with nuclear fast red (McGee-Russell, 1955) only after microincineration of the sections, a behaviour characteristic of calcium oxalate. A positive reaction to the silver-rubeanic acid method introduced by Yasue (1969) (Fig. 5) and to quinalizarin, but not alizarin red S, confirmed the presence of oxalate.

X-ray diffraction study of crystals removed from one of the subretinal outcrops showed a pattern characteristic of calcium oxalate monohydrate (Fig. 6, overleaf).

Discussion

Because the crystals form on the deep surface of detached retinæ they are not susceptible to detection by ophthalmoscopic examination so that the recognition of retinal oxalosis is of necessity a pathological diagnosis. There is no way of telling when the deposition began,

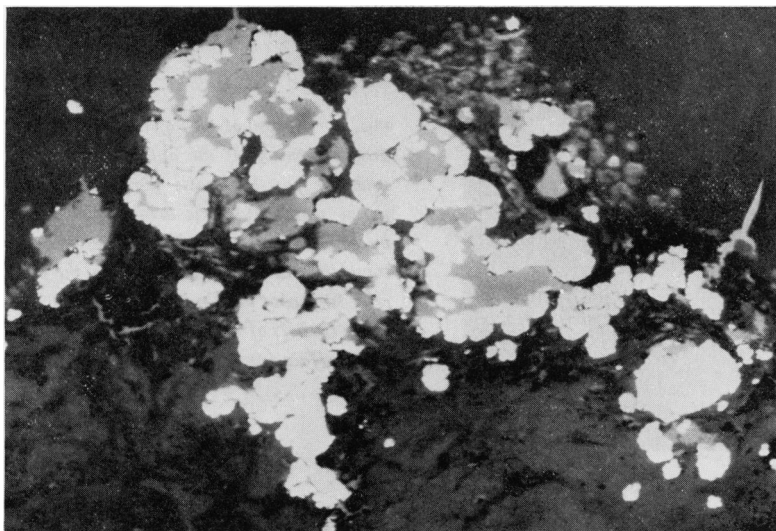


FIG. 4 When viewed between crossing polarizing screens, the crystals on the outer surface of the detached retina are strongly birefringent. $\times 76$

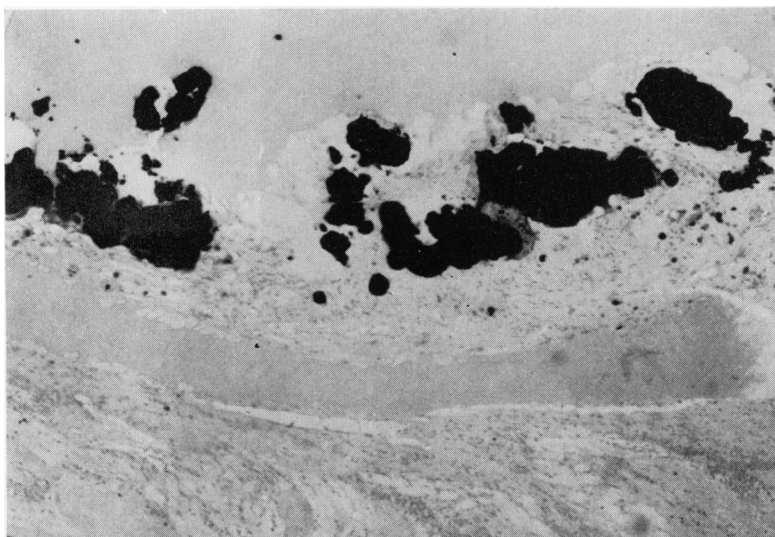


FIG. 5 Retinal crystals stained black in Yasue's silver reaction for calcium oxalate. Silver-rubeanic acid. $\times 76$

although my experience and that of others that oxalates are not found in recently detached retinæ almost certainly means that deposition is a long-term complication in degenerate tissue. The sheaf-like grouping of the crystals suggests, moreover, that once seeding or nucleation has occurred subsequent growth is rapid, while their location suggests that they are likely to be derived from soluble calcium oxalate in the subretinal exudate.

Apart from exogenous oxalic acid present in certain foods, there are two metabolic sources of oxalate. One is through the oxidation of glyoxylic acid which, in turn, is derived principally from the catabolism of the amino-acid glycine (Fig. 7). Increase in oxalate from this source is facilitated by deficiency of either pyridoxine (Faber, Feitler, Bleiler, Ohlson, and Hodges, 1963) or thiamine (Buckle, 1963). The accidental or suicidal imbibing of ethylene glycol can also act as a source of glyoxylic acid (Friedman, Greenberg, Merrill, and Dammin, 1962). Primary hyperoxaluria exists in two forms determined by an inherited

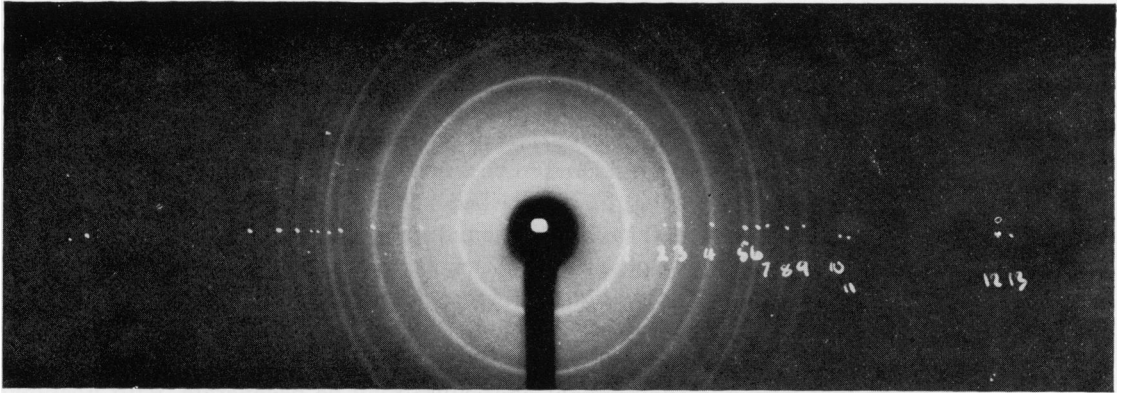


FIG. 6 X-ray diffraction pattern of a crystal removed from the outer surface of the detached retina

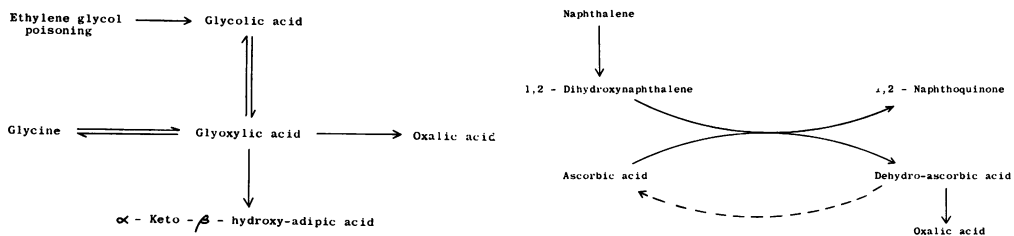


FIG. 7 Glyoxylic acid pathway. The re-conversion of glyoxylic acid to glycine is pyridoxine-dependent, while the formation of α -keto- β -hydroxyadipic acid requires thiamine and is impaired in one type of primary hyperoxaluria. The ultimate fate of the latter product is as yet unknown

FIG. 8 Ascorbic acid pathway. Ascorbic acid normally undergoes a continuous cycle of oxidation and reduction but any circumstances which cause excessive oxidation, such as follows the experimental administration of naphthalene will result in increased oxalate synthesis

deficiency of either of two enzymes concerned in the degradation of glyoxylic acid (Williams and Smith, 1972). All forms of oxalosis linked to the glyoxylic acid metabolic pathway are, however, part of a generalized disturbance which predisposes to crystal deposition in the kidneys and a number of other organs. Apart from a single case of primary oxalosis referred to earlier, ocular involvement in hyperoxaluria due to abnormal glyoxylate metabolism has not been recorded, while, conversely, neither in the present case nor in other reports of retinal oxalosis, is there any evidence of systemic involvement.

A second endogenous source of oxalate, which normally accounts for just under half the daily output, involves the oxidation of ascorbic acid (Baker, Saari, and Tolbert, 1966) and in this context it may be relevant to note that ocular fluids have an unusually high content of ascorbic acid (Purcell, Lerner, and Kinsey, 1954). Furthermore, it may be significant that the only experimental form of ocular oxalosis to have been recorded involved the feeding of naphthalene to rabbits: this promoted undue oxidation of ascorbic acid to oxalic acid (Fig. 8), which was subsequently deposited as calcium oxalate in the outer retina (van Heyningen and Pirie, 1967; Pirie, 1968). This observation raises the possibility that the oxalosis which complicates exceptional instances of retinal detachment and cataract in man may also operate through ascorbic acid metabolism. The pH elevation associated with tissue degeneration could facilitate crystal deposition, since calcium oxalate is highly insoluble in an alkaline milieu.

Iatrogenic forms of oxalosis are also recorded. Thus both the intravenous infusion of xylitol (Thomas, Edwards, Gilligan, Lawrence, and Edwards, 1972; Evans, Phillips, Mukherjee, Snow, Lawrence, and Thomas, 1973) and the use of methoxyflurane as a general anaesthetic (Paddock, Parker, and Guadagni, 1964; Mazze, Trudell, and Cousins, have been reported as causing calcium oxalate deposition in the kidneys and other tissues. In these instances the oxalate is considered to be a metabolite of the substances themselves. Recently, Bullock and others (1973) have described calcium oxalate crystals in the pigment epithelium of the retina in a fatal case of methoxyflurane-provoked oxalosis. The cause of the selective involvement of the pigment is not explained, although it could conceivably reflect the known toxic effect of fluoride, a further derivative of methoxyflurane, on this structure (Sorsby and Harding, 1960; Orzalesi, Grignolo, and Calabria, 1967). In the context of the oxalate deposition which complicates long-standing retinal detachment, it may be noted that here also the pigment epithelium may be degenerate, with liberated melanin lying in proximity to the crystals, while experiments in the rat by Cook and Henderson (1969) using radioactive tracers have shown that the melanin precursors phenylalanine and tyrosine can be converted to oxalate. Although it does not appear to involve glyoxalate synthesis, the pathway concerned in this degradation has not been defined. Should it prove, however, that oxaloacetate and fumarate are involved as intermediate products, this would be of particular interest in view of the finding that such a mode of tyrosine breakdown is facilitated by the presence of ascorbic acid (La Du and Gjessing, 1972). Finally, since thyroxine is another substance based on tyrosine, it may not be without relevance that calcium oxalate crystals have been reported as a common finding in the colloid of ageing thyroid glands (Richter and McCarty, 1954).

Summary

Pathological examination of an eye removed because of long-term complications after traumatic perforation of the cornea revealed the presence of calcium oxalate crystals in the outer layers of a detached and degenerate retina. Analysis of the crystals was based on their histochemistry and x-ray diffraction pattern. The pathogenesis of oxalate deposition in this situation is obscure but some of the possibilities are outlined.

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